

## Validity of protein-creatinine and protein-osmolality ratios in the estimation of massive proteinuria in children with nephrotic syndrome

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### Abstract

**Background** Children with nephrotic syndrome have massive proteinuria, a rate of excretion equal to or greater than 40 mg/hour/m<sup>2</sup> body surface. The ability to quantitate massive urinary protein excretion is very important for both diagnostic and prognostic purposes. Quantification of proteinuria using 24-hour urine collection (Esbach) is difficult to do especially in children; moreover, many false-positive and false-negative results are reported for any semi-quantitative methods such as dipstick and sulfosalicylic acid measurement.

**Objective** To determine the accuracy of protein-creatinine ratio (PCR) and protein-osmolality ratio (POR) in quantification of massive proteinuria in children with nephrotic syndrome.

**Methods** Diagnostic tests were conducted on children with nephrotic syndrome aged 2-12 years with Esbach as a reference standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value, (NPV), pre and posttest probability were compared between PCR and POR.

**Results** Study patients consisted of 47 children, 38 (81%) with massive proteinuria. PCR has sensitivity of 92%, specificity of 78%, PPV of 95%, NPV of 70% and posttest probability of 95%. POR has sensitivity of 76%, specificity of 78%, PPV of 94%, NPV of 44% and posttest probability of 94%.

**Conclusion** Both PCR and POR are accurate to determine massive proteinuria in children with nephrotic syndrome. [Paediatr Indones 2007;47:139-143].

**Keywords:** nephrotic syndrome, protein-creatinine ratio, protein-osmolality ratio

Proteinuria is an important sign of kidney disease. The most common disease with proteinuria is nephrotic syndrome (NS). Massive proteinuria is a primary symptom of NS, while other symptoms are secondary manifestation of massive proteinuria.<sup>1-3</sup> Massive proteinuria was determined by Esbach test, which is a gold standard for proteinuria measurement. This quantitative measurement is difficult to apply in children because of difficulty in performing 24-hour or overnight urine collection. This measurement is also impractical and inconvenient.<sup>4,5</sup> Other method for determining proteinuria is qualitative method using dipstick and sulphosalicylic acid (SSA) which use random urine samples. The disadvantage of these tests is that they are affected by urine volume, which may lead to false positive or false negative results.<sup>6-8</sup>

Proteinuria can also be examined using protein-creatinine ratio (PCR) and protein-osmolality ratio (POR) tests. Both are semi quantitative tests, using random urine samples.<sup>9,10</sup> The disadvantage of PCR

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test is that creatinine excretion fluctuates in severe glomerular damage, which may affect PCR value. Compared with POR, PCR test is more difficult to do and expensive.<sup>11-13</sup> PCR and POR could be an alternative modalities to determine massive proteinuria. The purpose of this study was to investigate the accuracy of protein-creatinine ratio (PCR) and protein-osmolality ratio (POR) in quantification of massive proteinuria in children with nephrotic syndrome.

## Methods

The was a diagnostic study done in 2005 using all nephrotic syndrome (NS) patients of initial, relapses, remission status, treated at the Nephrology Division, Department of Child Health, Udayana University/Sanglah Hospital. The inclusion criteria were NS patients aged 2-12 years old whom the proteinuria screening test using SSA gave positive result. The exclusion criteria were (1) macroscopic hematuria, (2) acute renal failure, (3) chronic renal failure, (4) severe malnutrition, (5) using trimetoprim-sulfametoxazole, antacida, probenecid, (6) not able to perform overnight urine collection, (7) parents refused to participate in this study. We enrolled subjects consecutively.

A pediatric resident in charge recorded age, sex, body weight, body height, diagnosis, urinalysis results and then performed a complete physical examination on admission. Every patient underwent three methods of proteinuria measurements, i.e., Esbach test using overnight urine collection, PCR and POR using casual urine specimen. Protein-creatinine ratio value was determined by dividing quantitative proteinuria (Meditron-M<sup>®</sup>) with urine creatinine (Hitachi 912<sup>®</sup>), while protein-osmolality ratio value was determined by dividing quantitative proteinuria (Meditron-M<sup>®</sup>) with urine osmolality. We counted urine osmolality using formula: (urine specific gravity – 1.000) x 40,000. These tests were done by an analyst who didn't concern about the study.

Based on Esbach test result, patients were divided into two groups: massive proteinuria (if protein in urine was more than or equal to 40 mg/body surface/hour) and non massive proteinuria groups. PCR and POR were described in numeric scales; therefore a cut-off value with receiver operator characteristic

(ROC) curve was done (as seen in **Figures 1** and **2**). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, pre and post-test probability (PTP) with confidence interval (CI) 95% analyzed by computer.

Approval from the Ethical Research Committee, Research & Development Unit of Udayana University, Sanglah Hospital, Denpasar was obtained.

## Results

During the study period, 10 patients (one patient suffered from acute renal failure and the other nine had incomplete overnight urine collection for Esbach examination) were excluded.

Eight of the 47 patients were initial NS patients and 39 were relapse NS. One patient was secondary NS caused by Autoimmune Hemolytic Anemia (IAHA) and the others were primary NS. Thirty eight patients suffered from massive proteinuria. No one was reported to suffer from multiple myeloma, rhabdomyolysis, or heavy activity before proteinuria tests. One patient suffered from fever, two patients got albumin infusion due to hypovolemic shock, another two had hypertension and five patients were obese. All conditions were found in massive proteinuria group. Basic characteristics between massive and non massive proteinuria groups are shown in **Table 1**.

According to ROC curves, the cut-off point of PCR was 2.1 (area under the curve 0.863, **Figure 1**) and POR was 0.281 (area under the curve 0.803, **Figure 2**) with the best sensitivity and specificity value. The sensitivity, specificity, PPV, NPV, accuracy and likelihood ratio of PCR and POR are shown in **Table 2**. It is shown that both PCR and POR can be used as a diagnostic tool to determine massive proteinuria in children with NS.

## Discussion

Proteinuria is an essential sign of renal failure. Measurement of proteinuria is important in diagnosing renal disorder and to know the treatment response.<sup>14,15</sup> Massive proteinuria usually occurs in glomerular disorder, where the highest rate is in NS. In NS, proteinuria is severe, and this is a base for diagnosing NS.<sup>16-18</sup>

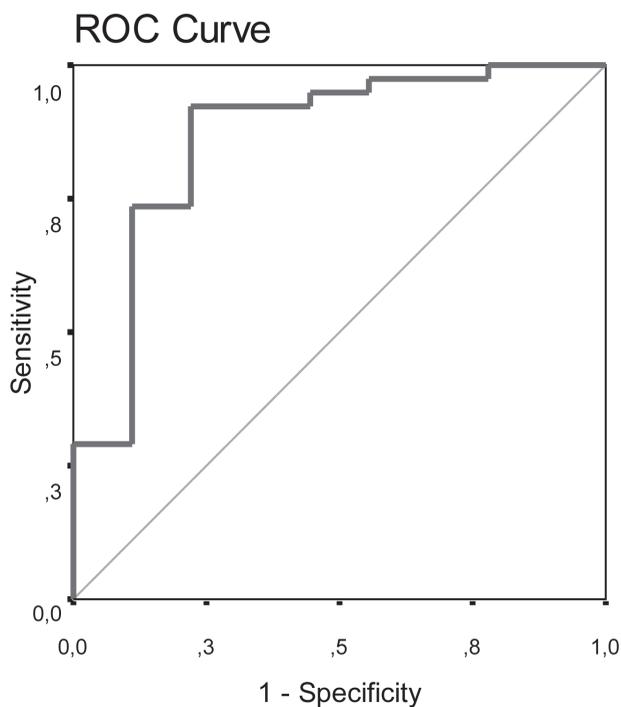
**Table 1.** Baseline characteristics of the patients

Characteristics	Massive proteinuria n=38	Non Massive proteinuria n=9
Boys, n	19	2
Age, year, mean (SD)	5.2 (2.6)	6.1 (2.7)
Body weight, kg, mean (SD)	22.3 (8.8)	25.2 (7.7)
Height, cm, mean (SD)	110.5 (16.1)	117.3 (15.8)
Fever, n	1	0
Infused with albumin, n	2	0
Hypertension, n	2	0
Obesity, n	5	0
Overnight proteinuria, g/dl, mean (SD)	5 (13.2)	0.18 (0.07)
Urine creatinine, mg/dl, mean (SD)	75.67 (53.56)	62.54 (30.23)
PCR, mean (SD)	6.39 (5.39)	1.95 (2.03)
Urine specific gravity, mean (SD)	1.0137 (0.0043)	1.0122 (0.0044)
Urine osmolality, mOsm, mean (SD)	548.42 (174.20)	488.88 (176.38)
POR, mg/dl/mOsm, mean (SD)	0.64 (0.36)	0.27 (0.38)

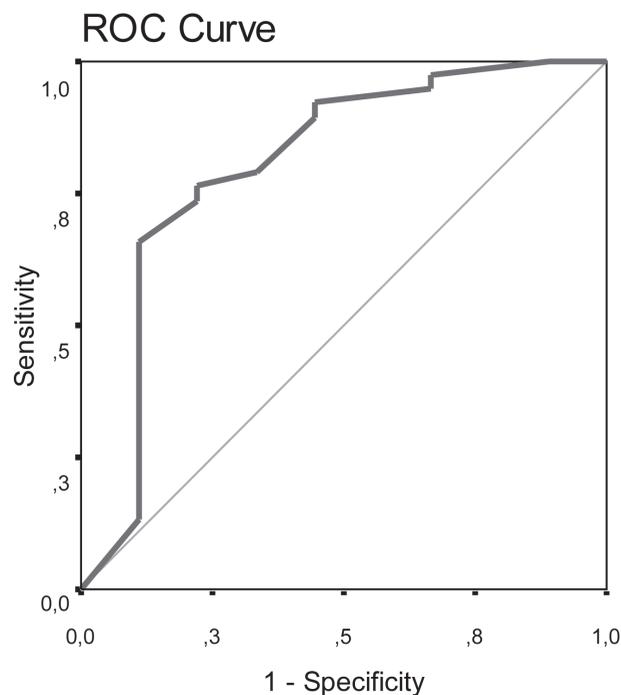
**Table 2.** The sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratio of PCR and POR

Examination	Sen (%) (CI 95%)	Spe (%) (CI 95%)	PPV (%)	NPV (%)	Accuracy	PLR (+) (CI 95%)	Prev (%)	PTP (%)
PCR	92.11 (80.00-97.95)	77.78 (43.79-96.09)	94.59	70.00	89.36	4.14 (1.22-14.12)	80.85	94.59
POR	76.32 (60.97-87.78)	77.78 (43.79-96.09)	93.55	43.75	76.59	3.43 (1.00-11.81)	80.85	93.55

Note: Sen : sensitivity, spe: specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value, PLR (+): Positive Likelihood Ratio, Prev: Prevalence, PTP: Post Test Probability



**Figure 1.** Receiver operator characteristic curve of PCR



**Figure 2.** Receiver operator characteristic curve of POR

There are some methods to determine massive proteinuria. The easiest is by dipstick test or SSA using spot urine sample. The disadvantage of these tests is they are influenced by urine volume.<sup>6-8</sup> Measurement with Esbach using 24-hour urine collection is the best method to determine massive proteinuria. To avoid orthostatic and intermittent proteinuria, 24-hour urine collection usually replaced by overnight urine collection, which has the same accuracy.<sup>4-5</sup> This quantitative test is difficult to perform in children especially in those who can't control urination. Mistakes often happen during calculating the time and while accommodating the urine.<sup>1,3</sup>

The disadvantage of Esbach test and qualitative test (dipstick and SSA) is that they are not accurate. The alternate ways to measure massive proteinuria are PCR and POR which are semi quantitative test.<sup>9,10</sup> The excretion of creatinine is relatively constant, but sometimes it fluctuates in severe glomerular failure that can influence the result.<sup>10</sup> This test can also be influenced by tubular failure as the tubular excretion increases creatinine excretion. In several centers, osmolality is measured using osmometer, which gives fast result. Compared to PCR, POR test is cheaper and easier.<sup>11,12</sup>

Until this time, there are some views over the value of PCR and POR tests. In this study, we used 47 patients, 21 were male and 8 were initial NS cases. One patient suffered from secondary NS caused by AIHA. We used samples age group older than two years with a hope that this age group can already control urination. Other conditions which can cause proteinuria like fever, hypertension, heavy activities, congestive heart failure, obesity and overload proteinuria were not excluded because they only cause mild proteinuria.<sup>1,19</sup> Nephrotic syndrome with gross hematuria and renal failure were excluded to homogenize the samples.

In this study, we found cut-off point of 2.1 in PCR with 92.11% sensitivity and 77.78% specificity, and of 0.281 in POR, which has 76.32% sensitivity and 77.78% specificity.

Kim *et al*<sup>11</sup> reported that PCR more than 1.5 and POR more than 0.23 represent nephrotic-range proteinuria. PCR had PPV of 100% and NPV of 97.5%, while POR had PPV of 92.3% and NPV of 90%. This difference might be caused by the difference samples and laboratory tests used. In Kim study, the samples used were all patients with kidney dis-

orders who came to nephrology clinic, aged 1 month to 15 years old, using 24-hour urine collection on Esbach test and measurement of osmolality urine using osmometer.

Hooman *et al*<sup>12</sup> found cut-off point of 1.59 for PCR and 1.02 for RPO to diagnose nephrotic-range proteinuria, with equal sensitivity (80.0%) and specificity of 90.2% for PCR and 84.4% for POR. This difference results might be caused by the samples used (Hooman used patients with all kidney disorders aged 1-17 years old, without excluding patients with renal failure), using 24-hour proteinuria as a gold standard and using osmometer for osmolality test. Systematic review of 16 studies on preeclampsia and renal disease subjects showed PCR with sensitivity of 69-96% and specificity of 41-97%. This test has proved to be useful in ruling out proteinuria.<sup>13</sup>

In this study, we found that LR (+) were 4.14 in PCR and 3.43 in POR, which showed that both tests are good enough. Positive LR means the possibility of the person with disease to get a positive result compared with healthy person with the same result. A moderate result gives a value around one. This used prevalence to determine post test probability.<sup>20</sup> In this study, we found that PTP (Post Test Probability) of PCR and POR were 94.59% and 93.55%, respectively. These were quite a good results. This showed that both measurements are accurate for determining massive proteinuria.

Through this study we found that PCR test is better than POR test. This can be possible because: (1) The samples were NS patients with mild degree of glomerular damage, which does not influence the creatinine excretion. Most of NS in children (66-88%) have pathology anatomy of minimal changes.<sup>2,6</sup> (2) The samples did not suffer from tubular disorder that can increase creatinine excretion. (3) The osmolality value is calculated by indirect method that is through specific gravity. The best method to measure osmolality is through osmometer, yet this test is not available in the study center.

When we look at the cost of these tests, PCR has a cost of Rp. 44,500,-, while POR needs Rp. 22,500,- and Esbach needs Rp. 17,500,-. The price was slightly different.

The limitations of this study were: (1) Glomerular filtration rate (GFR) was not conducted. By excluding NS patients with renal failure we assumed that the

samples we used had normal GFR. (2) We used indirect method to measure urine osmolality. (3) In outpatients clinic, overnight urine collection for Esbach test was done by parents. We knew the complicity of the urine collection only from parents report.

We conclude that PCR and POR are accurate instruments to determine massive proteinuria in pediatric patients with nephrotic syndrome. PCR test has better sensitivity and accuracy than POR test.

### Acknowledgments

We would like to express our gratitude to Mr. Raka Widiana, MD, SpPD from Department of Internal Medicine, and Mr. IB Subanada, MD, SpA from Department of Child Health, Medical School, Udayana University, Denpasar, Bali, for their guidance in study methodology and statistical analysis.

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